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Preservation of Regional Myocardial Function and Myocardial Oxygen Tension During Acute Ischemia in Pigs: Comparison of Selective Synchronized Suction and Retroinfusion of Coronary Veins to Synchronized Coronary Venous Retroperfusion

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Objectives. **The efficacy of selective synchronized suction and retroinfusion of coronary veins was compared with synchronized coronary venous retroperfusion in preventing ischemic reduction of regional myocardial function and myocardial oxygen tension.**

Background. **Because incomplete protection by synchronized coronary venous retroperfusion during ischemia might result from nonselective retroinfusion and only passive drainage of the veins, a suction device was added to a retroinfusion system.**

Methods. **Regional myocardial function (ultrasonic crystals) and myocardial oxygen tension (polarographic electrodes) were studied in 30 pigs during 10-min occlusion of the left anterior descending coronary artery (ischemia), followed by reperfusion. During ischemia, group A (n = 10) was supported by selective synchronized suction and retroinfusion; group B (n = 10) was supported by synchronized coronary venous retroperfusion, and group C (n = 10) was not supported by retroinfusion.**

Results. **In group A, subendocardial segment shortening decreased from 21 ± 4% (mean ± SD) before ischemia to 11 ± 5% during ischemia. In contrast, systolic dyskinesia was observed in group B (−2 ± 4%, $p < 0.001$) and group C (−2 ± 5%, $p < 0.001$). During ischemia, the decrease in intramyocardial oxygen tension was less pronounced in group A (41 ± 15 vs. 27 ± 12 mm Hg) than in group B (40 ± 10 vs. 19 ± 10 mm Hg, $p = 0.1$) or group C (33 ± 11 vs. 12 ± 8 mm Hg, $p = 0.002$). During ischemia, myocardial surface oxygen tension was preserved >0 mm Hg only in group A.**

Conclusions. **Preservation of regional myocardial function and myocardial oxygen tension was substantially higher by selective synchronized suction and retroinfusion of coronary veins than by synchronized coronary venous retroperfusion in pigs.**

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Recent clinical studies have shown that synchronized coronary venous retroperfusion partially reduced ischemia during percutaneous transluminal coronary angioplasty (1,2). The efficacy of synchronized coronary venous retroperfusion, however, was far too low to completely prevent ischemic changes, such as loss of regional myocardial function or the development of chest pain during coronary artery angioplasty of normal duration (1). Incomplete protection by synchronized coronary venous retroperfusion during ischemia might be due to nonselective retroinfusion and only passive drainage of the veins. During synchronized coronary venous retroperfusion, retrograde catheterization is restricted to veins of sufficient size that do not hamper passive venous drainage around the balloon at the catheter tip. Therefore, it is not possible to selectively retroinfuse the ischemic myocardium. Furthermore, the passive drainage of the veins by systolic squeezing implies that with each diastolic pumping stroke the remaining venous blood or desaturated arterial blood is pumped retrograde before oxygen-saturated arterial blood fills the veins and reaches the microcirculation (3). To exchange the blood more effectively with each pumping stroke and to increase the probability of reaching the microcirculation by retroinfusion, we added an electrocardiographically synchronized suction device to a retroinfusion system (4). Reducing the coronary venous pressure distal to the catheter tip by active suction without deflating the balloon should make it possible to perform selective synchronized suction and retroinfusion in small coronary veins. Thus, the vein that drains the ischemic

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myocardium may be selectively catheterized, and the arterial blood may be retroinfused into an empty venous system. The closer approach to the ischemic myocardium and the more complete blood exchange might increase the efficacy of selective synchronized suction and retroinfusion of coronary veins compared with that of synchronized coronary venous retroperfusion. The aim of the present study was to test this hypothesis by determining regional myocardial function and myocardial oxygen tension during ischemia and reperfusion supported either by selective synchronized suction and retroinfusion of coronary veins or by synchronized coronary venous retroperfusion in pigs.

Methods

This study was approved by the Bavarian Animal Care and Use Committee and conformed to guidelines defined by the National Institutes of Health and the Food and Drug Administration.

Experimental preparation. Thirty German farm pigs weighing 20 to 33 kg (mean weight 25 kg) were premedicated with an intramuscular injection of ketamine (15 mg/kg body weight), atropine (0.5 mg) and midazolam (0.35 mg/kg). After endotracheal intubation, anesthesia was maintained by a mixture of Ethrane (enflurane) (1 to 1.5%), nitrous oxide and oxygen in the inspired air in addition to intravenous application of piritramid (10 mg/h), midazolam (10 mg/h) and pancuronium bromide (4 mg/h). Ventilation was adjusted to maintain arterial partial pressures of oxygen (Pao_2) and carbon dioxide ($Paco_2$) and pH within the following ranges: 100 mm Hg < Pao_2 < 180 mm Hg; 30 mm Hg < $Paco_2$ < 40 mm Hg; 7.3 < pH < 7.5.

A 5F thermodilution catheter was introduced through the right external jugular vein into the pulmonary artery to determine cardiac output. Two 6F Millar microtip catheters were introduced through the carotid arteries and positioned in the aortic arch and left ventricle to measure aortic blood pressure, left ventricular pressure and its first derivative (dP/dt). Two 7F catheter introducers were inserted through the left femoral and right internal jugular veins for administration of anesthetic drugs and fluids.

Access to the heart was achieved by sternotomy and a left thoracotomy in the fourth intercostal space. The pericardium was opened, and the left anterior descending coronary artery was dissected free. A snare was placed around it immediately distal to its first diagonal branch. In the pigs treated by selective synchronized suction and retroinfusion (group A) and in control pigs (group C), a 7F catheter introducer was placed in the interventricular vein. In these pigs the venous blood was drained at atmospheric pressure and was returned to the animal through the left jugular catheter introducer with a roller pump. In the pigs treated by synchronized coronary venous retroperfusion during ischemia (group B), an 8.5F catheter introducer was inserted through the left internal jugular vein. To avoid obstruction of the great cardiac vein by the 8.5F retroperfusion catheter, a

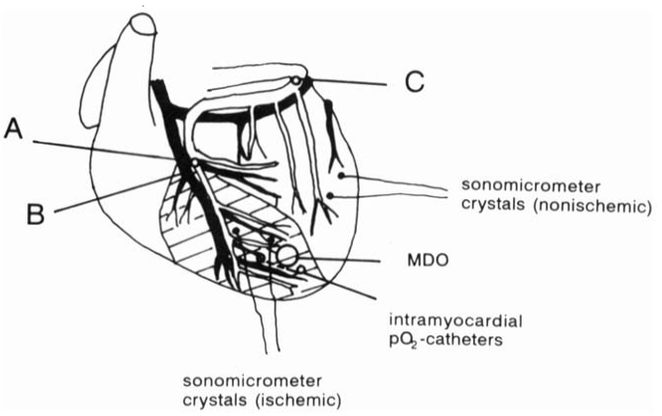

Figure 1. Scheme of experimental preparation. A = anterior interventricular vein, position of the retroinfusion catheter tip during selective synchronized suction and retroinfusion; B = occlusion site of the left anterior descending coronary artery; C = great cardiac vein, position of the retroperfusion catheter tip during synchronized coronary venous retroperfusion; MDO = multiwire oxygen surface electrode; pO_2 = arterial partial pressure of oxygen.

5F single-lumen catheter was advanced first through the coronary sinus into the great cardiac vein to measure intravascular pressure. Thereafter, the 5F catheter was replaced by the 8.5F triple-lumen retroperfusion catheter. After comparing the pressure readings obtained from the 5F and 8.5F catheters, the latter was advanced into the great cardiac vein as close as possible to the planned ischemic zone without changing mean coronary venous pressure by >5 mm Hg. Thus, peak pressures ([5F catheter] 18 ± 7 [mean ± SD] vs. [8.5F catheter] 20 ± 6 mm Hg, n = 10) and mean pressures ([5F catheter] 12 ± 7 vs. [8.5F catheter] 14 ± 6 mm Hg) of the great cardiac vein were similar after positioning of the 8.5F retroperfusion catheter. Contrast material was manually injected through the infusion lumen of the catheter into the great cardiac vein to confirm both adequate catheter positioning and proper occlusion of the great cardiac vein by the balloon. In one pig from group B, it was necessary to place the retroperfusion catheter in the coronary sinus to avoid obstruction of the great cardiac vein. In this pig, the azygos vein draining into the coronary sinus was ligated. In all pigs the position of the tip of the retroperfusion catheter was confirmed at necropsy. After instrumentation, all pigs received 300 IU/kg of sodium heparin intravenously, followed by 100 IU/kg after 2 h.

Regional myocardial function. Two pairs of 5-MHz ultrasonic crystals (2 mm in diameter) were implanted subendocardially in the anterior and lateral left ventricular wall. One pair was positioned distal to the planned occlusion site (planned ischemic zone) (Fig. 1) in the subendocardial layer, 10 to 15 mm apart and oriented parallel to the short heart axis for measurement of segment length. The second pair was placed subendocardially in the lateral wall (nonischemic zone) (Fig. 1). The correct position of the ultrasonic crystals was confirmed at necropsy. Segment lengths were measured with a sonomicrometer, and percent systolic segment short-

ening (%SS) was calculated from the following formula: %SS = [(EDL − ESL)/EDL] × 100, where EDL = end-diastolic length and ESL = end-systolic length. End-diastolic lengths were measured at the beginning of the upstroke of left ventricular dP/dt. End-systolic lengths were measured 20 ms before peak negative dP/dt. All variables of contractility were averaged over five cardiac cycles at each time point.

Myocardial oxygen tension. Because gradients of oxygen tension from the epicardium to the endocardium have been previously demonstrated (5–7), surface and intramyocardial oxygen tension were measured simultaneously in this study. For determination of left ventricular surface oxygen tension, an eight-channel polarographic surface electrode (MDO) of the Clark type was used as described in detail elsewhere (8). In brief, an electrode holder embedded in a flexible silicone rubber disk was fixed on the surface of the left anterior wall (ischemic zone) (Fig. 1). The electrode was calibrated before the first measurement and then recalibrated every hour. For correction of Po_2 data, tissue temperature was measured continuously, and linear drift of the electrode was assumed.

For determination of intramyocardial oxygen tension in the anterior (ischemic zone) and lateral (nonischemic zone) ventricular wall, flexible polarographic Po_2 catheters (GMS, Germany) were used as described in detail elsewhere (4). The Po_2-sensitive tip of the catheter was inserted completely into the midmyocardial layer through a previously inserted silicon tube (650 μm in diameter). Analysis of Po_2 measurements was not started until 1 h after insertion because intramyocardial Po_2 decreased initially after insertion but reached stable values after 30 to 45 min. The decrease in intramyocardial oxygen tension immediately after insertion was due to an initial compression of the surrounding tissue by the Po_2 catheter. Histopathologic examination of tissue sections obtained from the myocardium surrounding the Po_2 catheter (results not shown) provides evidence that 1 h after insertion of the Po_2 catheter, this initial compression was more equally distributed in the surrounding tissue. The depth of insertion of the tip of the Po_2 catheters in the midmyocardial layer was measured after necropsy (mean depth 4.5 ± 1.6 mm). All Po_2 data were corrected for drift, tissue temperature and $t_{75\%}$ response time (45 ± 16 s) of the Po_2 catheter.

Electrocardiographically synchronized suction and retroinfusion of coronary veins. The retroinfusion system has been described in detail elsewhere (4). Briefly, the device consisted of an electronic consoie that activated the retroinfusion pump (Prominent, Germany) and a valve in front of the suction pump (Ameda, Switzerland) that was triggered by the electrocardiogram (ECG) (pericardial leads). Arterial blood was shunted from the left femoral artery with a 9.5F withdrawal catheter system (Gambro, Germany) to the infusion lumen of a 7F four-lumen catheter that was introduced into the anterior ventricular vein through the 7F introducer. The tip of the retroinfusion catheter was advanced until the end of the introducer without leaving it. This access, which

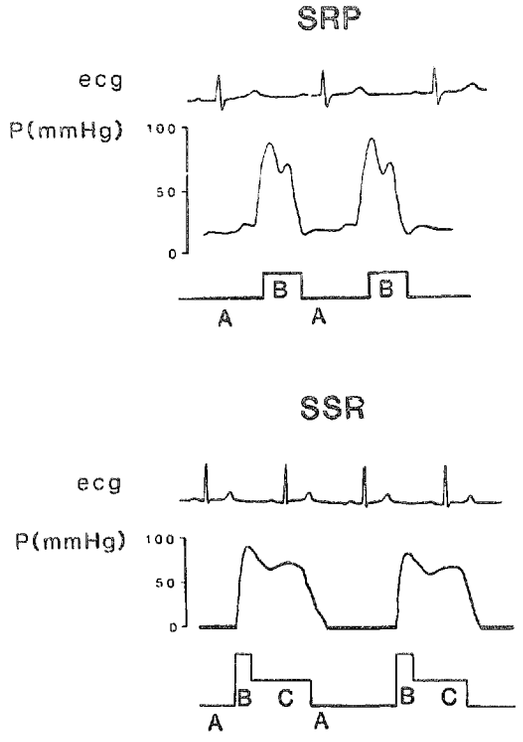

Figure 2. Scheme of electrocardiographically (ecg) triggered retroinfusion treatment during ischemia. **Top,** Synchronized coronary venous retroperfusion (SRP): A = balloon deflation; B = balloon inflation and pumping period. **Bottom,** Selective synchronized suction and retroinfusion of coronary veins (SSR): A = suction period; B = pumping period; C = period without suction or pumping. P = coronary venous pressure (derived from original tracings).

allowed venous drainage at atmospheric pressure before introducing the retroinfusion catheter, was used to avoid venous congestion before the start of selective synchronized suction and retroinfusion of coronary veins. Because of the stable position of the retroinfusion catheter within the introducer, blockage of the introducer lumen by inflation of the catheter balloon through the third lumen was not necessary. The fourth lumen of the retroinfusion catheter was used to monitor pressure.

Arterial blood was pumped every second diastole, followed by a period without pumping or suction until the end of the next systole (Fig. 2). The suction period lasted until the beginning of the next pumping stroke. With selective synchronized suction and retroinfusion of coronary veins, the retroinfusion volume was delivered on alternate beats because previous experiments showed that efficacy was similar but not higher with pumping on every beat. However, pumping on every beat at a heart rate >90 beats/min was accompanied by an increase in baseline, peak and mean diastolic venous pressures on every beat, indicating incomplete venous drainage as a consequence of too short a suction period. To maintain constant peak and mean diastolic pressures, the retroinfusion volume was delivered on alternate beats in these experiments. Within 15 s after start of retroinfusion, the pumped volume/beat was increased

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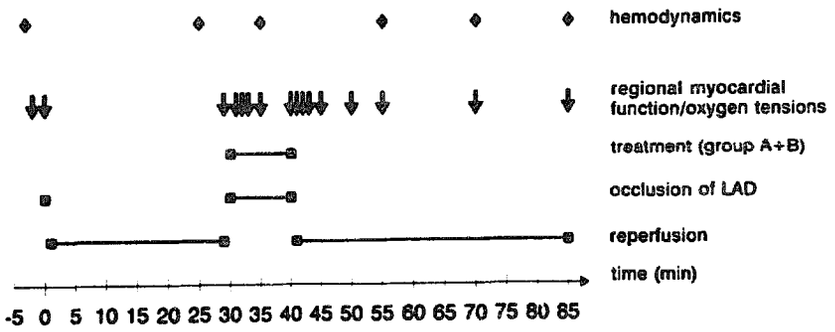

Figure 3. Study protocol and data acquisition. Group A = selective synchronized suction and retroinfusion of coronary veins; group B = synchronized coronary venous retroperfusion; LAD = left anterior descending coronary artery.

from 0.7 to 1.2 ml in steps of 0.1 ml unless coronary venous peak pressure exceeded 100 mm Hg. Thereafter, pump flow was kept constant during treatment with selective synchronized suction and retroinfusion.

Synchronized coronary venous retroperfusion. The retroperfusion system (Retroperfusion Systems Inc.) consisted of an ECG-gated pump connected to an 8.5F triple-lumen retroperfusion catheter, as previously described (1,9). The tip of the retroperfusion catheter was placed in the great cardiac vein (see Methods). The catheter balloon was inflated with carbon dioxide and arterial blood pumped during diastole (Fig. 2). During systole, the balloon was deflated to allow venous drainage. Within 15 s after the start of retroperfusion, mean flow was increased from 30 ml/min in steps of 5 ml, unless coronary venous peak pressure exceeded 100 mm Hg or mean coronary venous pressure exceeded 60 mm Hg (the upper safety limit of mean coronary venous pressure of the retroperfusion device preset by Retroperfusion Systems Inc.). Thereafter, pump flow was kept constant during treatment with synchronized coronary venous retroperfusion.

Experimental protocol and study groups. Control recordings of all variables were obtained after at least 30 min of stable conditions. In all 30 study animals, with the exception of 5 control pigs, the left anterior descending coronary artery was occluded (atraumatic vessel clip) for 1 min without treatment to confirm the correct position of the ultrasonic crystals and the multiwire surface electrode. Thirty minutes after the first occlusion of the left anterior descending coronary artery, a second occlusion of 10-min duration followed (Fig. 3). Pigs in Group A (n = 10) were treated by selective synchronized suction and retroinfusion of the anterior interventricular vein starting at the moment of occlusion of the left anterior descending coronary artery. Simultaneously, washed erythrocytes that were obtained from a previous pig from group C at the end of the experiment were transfused through the right external jugular vein at the same rate that blood was lost by the suction device. Hemoglobin content was similar before ischemia (8.4 ± 2 g/dl, mean ± SD) and after ischemia (8.6 ± 2 g/dl) in group A. Pigs in Group B (n = 10) were treated by synchronized retroperfusion of the great cardiac vein starting at the moment of occlusion of the left anterior descending artery. Pigs in Group C (n = 10) were not treated by retroinfusion during occlusion of the left anterior descending coronary artery. After 10 min of occlusion, in all pigs reperfusion of 50-min duration was performed by opening and removing the vessel clip (Fig. 3). If ventricular fibrillation developed during occlusion or reperfusion, defibrillation was attempted with direct current countershocks. However, no antiarrhythmic or other pharmacologic agents were delivered. After 50 min of reperfusion, the left anterior descending artery was occluded again, and 20 ml of 6% methylene blue solution was injected within 15 s through a previously inserted 5F catheter in the left atrium for determination of the left ventricular volume at risk. Thereafter, the heart was arrested by an intravenous overdose of potassium chloride and excised.

Postmortem studies. Hearts were removed, and small tissue blocks (1 to 2 mm in diameter) were cut from the anterior wall 0.5, 1.5 and 2.5 cm distal from the occlusion site of the left anterior descending coronary artery, including the anterior interventricular branches of the artery and vein. For transmission electron microscopy, these tissue blocks were immediately fixed by immersion in 2% glutaraldehyde. After washing in phosphate buffer for 2 h, tissue blocks were postfixed in 1% osmium tetroxide solutions for 2 h, dehydrated in ethanol series and embedded in an Epon-Araldite mixture. Ultrathin and semithin sections were cut on an ultramicrotome. Semithin sections were stained with toluidine blue. Ultrathin sections were stained with uramyl acetate and lead citrate. Sections were examined with an electron microscope (Zeiss, Germany).

For determination of the left ventricular volume at risk, 1-cm thick slabs were cut from apex to base and photographed as previously described (4). Thereafter, the slabs were immediately fixed in 10% phosphate-buffered formalin (pH 7.4). For light microscopy, three tissue blocks (1 to 2 cm in diameter) were cut from the anterior wall (ischemic zone) and the lateral and posterior ventricular walls (nonischemic zone). They then underwent further fixation and paraffin embedding. Thin sections were stained with hematoxylin-eosin, periodic acid-Schiff and van Gieson.

Data acquisition. Primary efficacy variables were regional myocardial function and myocardial oxygen tension. For assessment of efficacy, two variables were derived from serial measurement in time (Fig. 3) for each pig: 1) The mean of the last three values during the second occlusion of the left anterior descending coronary artery was calculated; and

Table 1. Hemodynamic Variables

	Baseline	Ischemia (5 min)	Reperfusion 15 min	Reperfusion 30 min	Reperfusion 45 min
Group A (n = 10, BW 23 ± 3 kg)					
CO (liters/min)	2.5 ± 0.6	2.4 ± 0.7	2.4 ± 0.6	2.5 ± 0.7	2.5 ± 0.5
HR (beats/min)	83 ± 11	79 ± 8	81 ± 5	79 ± 7	79 ± 8
MAP (mm Hg)	86 ± 9	81 ± 5	82 ± 6	82 ± 7	84 ± 8
LVEDP (mm Hg)	6 ± 4	6 ± 4	6 ± 5	5 ± 5	4 ± 5
Group B (n = 10, BW 25.3 ± 2.4 kg)					
CO (liters/min)	2.9 ± 0.3	2.3 ± 0.3*	2.4 ± 0.8*	2.5 ± 0.5*	2.5 ± 0.7*
HR (beats/min)	81 ± 9	83 ± 13	81 ± 11	83 ± 12	82 ± 12
MAP (mm Hg)	94 ± 13	70 ± 13*	73 ± 18	77 ± 15	78 ± 16
LVEDP (mm Hg)	8 ± 3	12 ± 6	6 ± 3	6 ± 5	5 ± 3
Group C (n = 10, BW 25.8 ± 2.9 kg)					
CO (liters/min)	2.4 ± 0.9	1.8 ± 0.7*	1.5 ± 0.5*	1.9 ± 0.9*	1.8 ± 1.1*
HR (beats/min)	90 ± 11	94 ± 13	94 ± 14	99 ± 11	99 ± 16
MAP (mm Hg)	82 ± 14	68 ± 15*	78 ± 14	79 ± 14	72 ± 15
LVEDP (mm Hg)	9 ± 2	13 ± 3*	10 ± 2	10 ± 2	9 ± 2

*$p < 0.05$ versus baseline value (during reperfusion mean values at 15, 30, and 45 min versus baseline). Values presented are mean value ± SD. BW = body weight; CO = cardiac output; Group A = pigs treated by selective synchronized suction and retroinfusion during occlusion of the left anterior descending artery (ischemia); Group B = pigs treated by synchronized retroperfusion during ischemia; Group C = pigs untreated during ischemia; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure.

2) the area under the curve for all values after the second reperfusion was calculated and presented as absolute value/minute (10). Hemodynamic variables were also used to assess efficacy (Fig. 3). During ischemia and reperfusion, the frequency of ventricular fibrillation was determined.

Statistics. The experimental data were analyzed with the use of BMDP (BMDP Statistical Software) and SAS (SAS Institute) software on a UNIX workstation. Because plots of the primary efficacy variables against time for each pig showed similar shapes, the mean values and standard deviations at each time point were used to summarize the serial measurements for each group. Similarity of groups was assessed by comparing body weight and baseline values of regional myocardial function, myocardial oxygen tension and hemodynamic variables (cardiac output, heart rate, mean arterial pressure, left ventricular end-diastolic pressure) using a nonparametric one-way analysis of variance (Kruskal-Wallis test). For assessment of efficacy, the variables derived from the primary efficacy variables were compared with use of a Kruskal-Wallis test. If the Kruskal-Wallis test was statistically significant ($p < 0.05$), each pair of groups was compared with the Mann-Whitney test to investigate differences between individual groups. Changes in hemodynamic variables within each group were analyzed by comparing the baseline value with the value obtained 5 min after the second occlusion of the left anterior descending coronary artery and the mean value obtained 15, 30 and 45 min after the second reperfusion (Fig. 3) with the use of a nonparametric two-way analysis of variance (Friedman test). If the Friedman test was statistically significant ($p < 0.05$), each pair of time points was compared with a Wilcoxon test to investigate differences between individual time points. Differences in coronary venous pressure between the groups during ischemia were analyzed with the use of the Mann-Whitney test. Differences in the proportions of ventricular fibrillation in the three groups were analyzed with the use of the Fisher exact test. All data are expressed as mean value ± SD, unless otherwise indicated.

Results

Similarity of study groups. The three study groups were similar in body weight (Table 1). No statistically significant differences were observed for baseline values of cardiac output, heart rate, mean arterial pressure, left ventricular end-diastolic pressure (Table 1), systolic segment shortening (planned ischemic and nonischemic region), myocardial surface oxygen tension and intramyocardial oxygen tension (planned ischemic and nonischemic regions). In pigs not treated during ischemia (group C), loss of regional myocardial function in the ischemic zone was similar (−1.1 ± 3.9% vs. −1.2 ± 3.5%) with (n = 5) and without (n = 5) a previous 1-min occlusion of the left anterior descending coronary artery. This suggests that the 1-min occlusion, followed by 29 min of reperfusion, had no effect on the decline of regional myocardial function after the second occlusion.

Primary efficacy variables: regional myocardial function and myocardial oxygen tension. During occlusion of the left anterior descending coronary artery, mean systolic segment shortening in the ischemic zone decreased from 21 ± 4% before ischemia to 15 ± 6% after 1 min of ischemia and to 11 ± 5% between minutes 3 and 10 of ischemia (see Methods) (Fig. 4A). In contrast to findings in group A, systolic dyskinesia was observed in group B (−2 ± 4%, $p < 0.001$) (Fig. 4B) and group C (−2 ± 5%, $p < 0.001$) (Fig. 4C) during ischemia. During ischemia, segment shortening in

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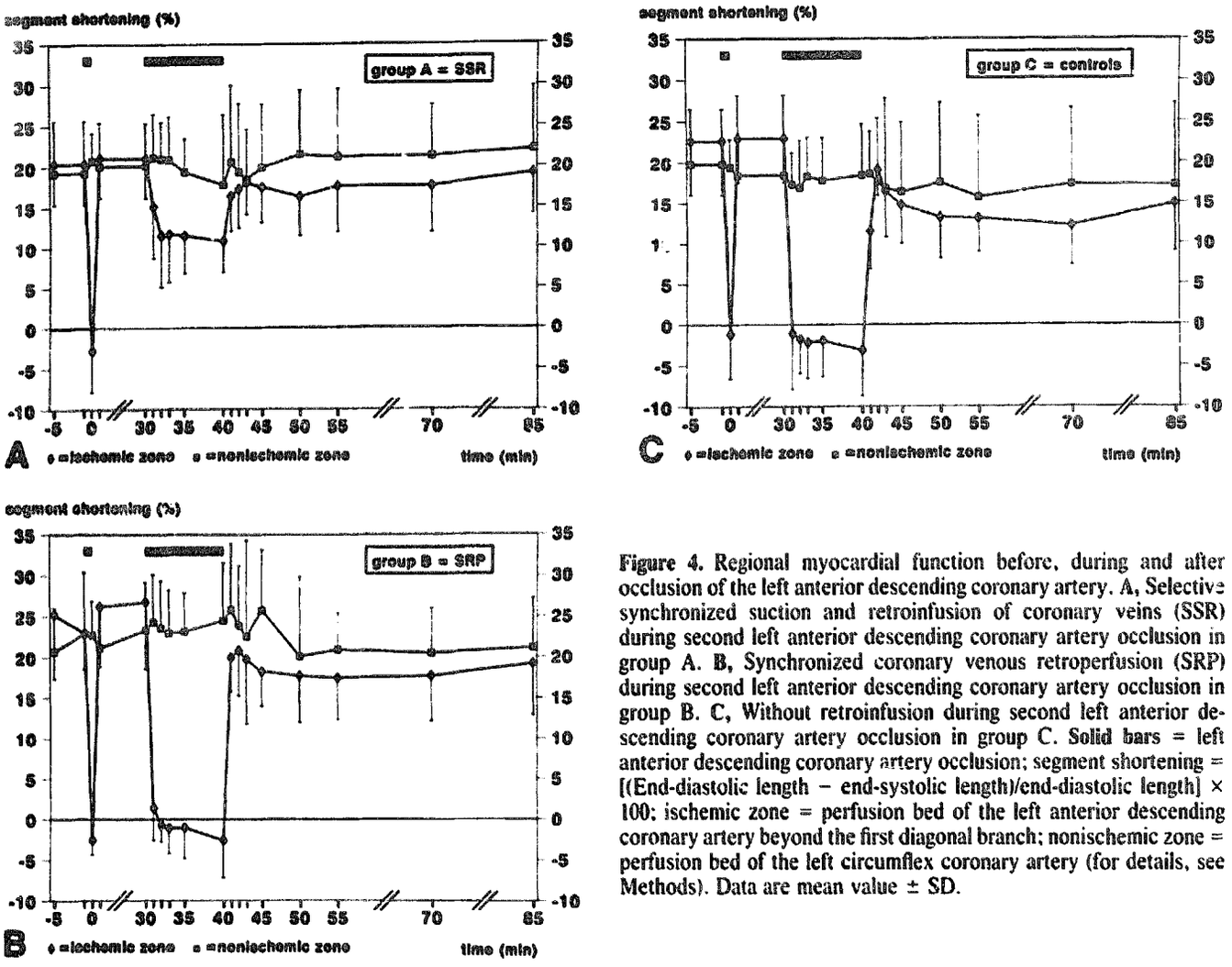

Figure 4. Regional myocardial function before, during and after occlusion of the left anterior descending coronary artery. A, Selective synchronized suction and retroinfusion of coronary veins (SSR) during second left anterior descending coronary artery occlusion in group A. B, Synchronized coronary venous retroperfusion (SRP) during second left anterior descending coronary artery occlusion in group B. C, Without retroinfusion during second left anterior descending coronary artery occlusion in group C. Solid bars = left anterior descending coronary artery occlusion; segment shortening = [(End-diastolic length − end-systolic length)/end-diastolic length] × 100; ischemic zone = perfusion bed of the left anterior descending coronary artery beyond the first diagonal branch; nonischemic zone = perfusion bed of the left circumflex coronary artery (for details, see Methods). Data are mean value ± SD.

group B was not significantly different from that in untreated control pigs (group C).

During reperfusion, the area under the curve (see Methods) was higher in group A (15 ± 7%/min, p = 0.23) and group B (17 ± 4%/min, p = 0.17) than in group C (12 ± 9%/min) (Fig. 4); however, these differences did not reach statistical significance. In the nonischemic zone, no differences in regional myocardial function were observed between the three groups during ischemia and reperfusion (Fig. 4).

Myocardial surface oxygen tension rapidly declined to zero during ischemia in group C, whereas intramyocardial oxygen tension decreased to 7.4 ± 7 mm Hg 10 min after occlusion of the left anterior descending coronary artery (Fig. 5C). In contrast to findings in groups B and C, myocardial surface oxygen tension in the ischemic zone did not decrease to zero values in group A (10 ± 11 mm Hg). Furthermore, during ischemia the decrease in intramyocardial oxygen tension was less pronounced in group A (41 ± 15 vs. 27 ± 12 mm Hg) compared with group B (40 ± 10 vs. 19 ± 10 mm Hg, p = 0.1) and group C (33 ± 11 vs. 12 ± 8 mm Hg, p = 0.002) (Fig. 5). During reperfusion, myocardial surface Po_2 and intramyocardial Po_2 (area under the curve) were not significantly different among the three groups (Fig. 5).

Additional efficacy variables. Hemodynamic variables are shown in Table 1. Five minutes after occlusion of the left anterior descending coronary artery, cardiac output was lower than the baseline value in groups B (p = 0.002) and C (p = 0.002). In group A no difference was observed. During reperfusion, cardiac output remained low in groups B (p = 0.002) and C (p < 0.001) compared with baseline values. During ischemia, mean arterial blood pressure decreased in groups B (p < 0.001) and C (p = 0.004) compared with baseline values. Left ventricular end-diastolic pressure increased during ischemia only in groups B (p = 0.03) and C (p = 0.001). During ischemia, ventricular fibrillation was more frequent in group C than in groups A and B (p = 0.08) (Table 2). During reperfusion, group B had the highest incidence of ventricular fibrillation (p = 0.1), which occurred predominantly in the early reperfusion period (min 1 to 5). Defibrillation was successful in all cases except for one pig from group A because of technical failure of the defibrillator. The duration of ventricular fibrillation was <30 s in all pigs.

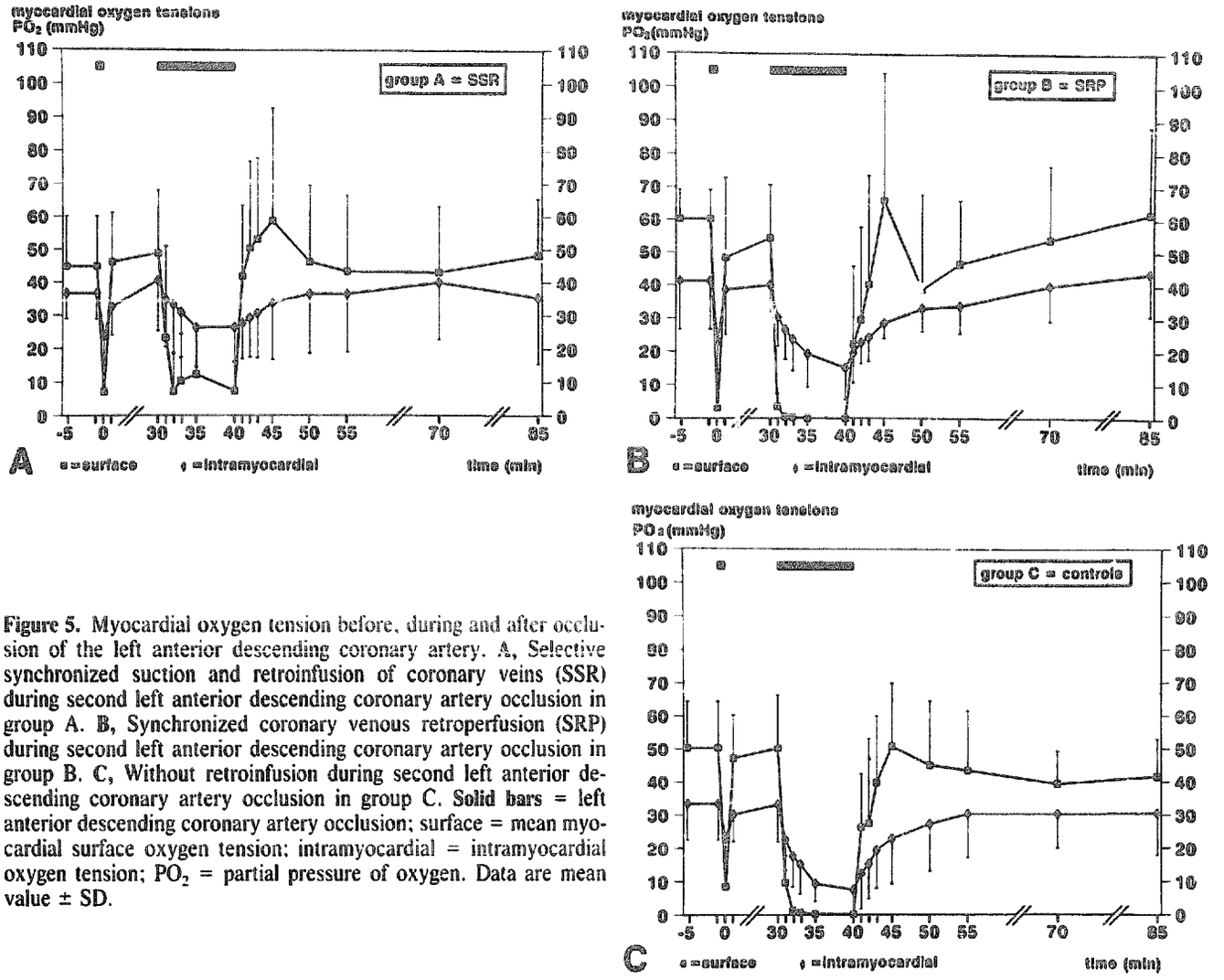

Figure 5. Myocardial oxygen tension before, during and after occlusion of the left anterior descending coronary artery. A, Selective synchronized suction and retroinfusion of coronary veins (SSR) during second left anterior descending coronary artery occlusion in group A. B, Synchronized coronary venous retroperfusion (SRP) during second left anterior descending coronary artery occlusion in group B. C, Without retroinfusion during second left anterior descending coronary artery occlusion in group C. Solid bars = left anterior descending coronary artery occlusion; surface = mean myocardial surface oxygen tension; intramyocardial = intramyocardial oxygen tension; PO_2 = partial pressure of oxygen. Data are mean value ± SD.

No antiarrhythmic drugs were delivered. In all groups, regional myocardial function did not change substantially between the measurements before and after ventricular fibrillation during ischemia or reperfusion (Table 2).

Effects of selective synchronized suction and retroinfusion of coronary veins and synchronized coronary venous retroperfusion on coronary venous pressure. Retroinfusion resulted in an increase in coronary venous pressure in pigs treated by retroinfusion during ischemia (groups A and B). During the pumped beats, diastolic peak and mean pressures were similar in group A (peak pressure 104 ± 17 mm Hg, mean pressure 63 ± 14 mm Hg) and group B (peak pressure 89 ± 24 mm Hg, mean pressure 61 ± 16 mm Hg). In group A, during unpumped beats, coronary venous pressure was reduced to zero by active suction. Therefore, mean coronary venous pressure was lower in group A (34 ± 14 mm Hg) than in group B (50 ± 17 mm Hg) (Table 3). Mean retroinfusion flows and retroinfusion flow/pumped beat were not

Table 2. Frequency of Ventricular Fibrillation

	Pigs (no.)	During Ischemia T(z) (min)	During Ischemia ΔSS (%)	Pigs (no.)	During Reperfusion T(z) (min)	During Reperfusion ΔSS (%)
Group A (n = 10)	1	2(8)	−5.4	2	3(5), 3(8)	−3.7 ± 5.2
Group B (n = 10)	2	6(3), 7(5)	−3.7 ± 5.2	7	1(2), 1(6), 1(7), 1(10), 3(1), 3(4), 5(3), 5(6), 7(10), 19(3), 28(3)	−3.7 ± 5.2
Group C (n = 10)	6	2(10), 3(3), 3(8), 4(1), 5(3), 6(1), 6(5), 7(8), 9(2)	1.0 ± 1.6	4	2(3), 2(8), 3(2), 3(4), 5(4)	−0.4 ± 5.7

Values presented are mean value ± SD or number. ΔSS = change in segment shortening before and after ventricular fibrillation. T = time point of ventricular fibrillation; (z) = no. of pig; other abbreviations as in Table 1.

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Table 3. Coronary Venous Pressure and Retroinfusion Flow

	Group A (n = 10)		Group B (n = 10)
	Pumped Beats	Unpumped Beats	Pumped Beats
Coronary venous pressure (GCV)			
Peak (mm Hg)	104 ± 17	27 ± 7	89 ± 24
Mean dia (mm Hg)	63 ± 14	7 ± 6	61 ± 16
Mean sys (mm Hg)	31 ± 13	0	33 ± 14
Mean dia + sys (mm Hg)	34 ± 14		50 ± 17
Min (mm Hg)	0	0	21 ± 8
Retroinfusion flow			
Mean flow (ml/min)	51 ± 15		63 ± 22
Flow/beat (ml)	1.1 ± 0.2	0	0.9 ± 0.3

Values presented are mean value ± SD. dia = diastolic; GCV = great cardiac vein; min = minimum; sys = systolic; other abbreviations as in Table 1.

statistically significant different between groups A and B (Table 3).

Pathologic findings. The volume at risk after occlusion of the left anterior descending coronary artery was similar in the three study groups: (42 ± 4%, 39 ± 6% and 41 ± 5% of the left ventricular volume in groups A, B and C, respectively). The distances between the occlusion site of the left anterior descending coronary artery and the entrance site of the ultrasonic crystals at the myocardial surface did not differ among the three groups, with a mean distance of 27 ± 6 mm to the entrance site of the first ultrasonic crystal and 33 ± 6 mm to the entrance site of the second ultrasonic crystal.

In the samples of the anterior ventricular groove (see Methods), a cross section of the left anterior descending coronary artery as well as the anterior ventricular vein was apparent. In about half of the veins, a thin bicuspid valve existed. In pigs treated with retroinfusion (groups A and B), no alterations of the veins (e.g., endothelial cell layer; basal membrane; subendothelial layers of veins, venules and capillaries) or of the surrounding tissue (e.g., hemorrhage, edema) were detected by light or electron microscopy.

Discussion

Experimental model. The aim of the study was to compare the efficacy of selective synchronized suction and retroinfusion of coronary veins with synchronized coronary venous retroperfusion in preventing the loss of regional myocardial function and reduction of myocardial oxygen tension in the setting of acute ischemia. Using a pig model of ischemia with the characteristic feature of rare collateral vessels and low collateral blood flow (11), myocardial sensitivity to ischemia was assumed to be higher or similar to that in humans. None of the previous retroperfusion catheter methods was able to significantly reduce the loss of regional myocardial function after complete arterial occlusion in pigs (12–14). In dog models with a residual blood flow through collateral vessels of approximately 20% to 25% of baseline values despite arterial occlusion (15), synchronized coronary venous retroperfusion was shown to be more effective than pressure-controlled intermittent coronary sinus occlusion (16–20). Therefore, synchronized coronary venous retroperfusion was chosen as the reference method to be compared with selective synchronized suction and retroinfusion of coronary veins in the present study. Compared with earlier studies with synchronized coronary venous retroperfusion in pigs (12–14,21), an improved device of synchronized coronary venous retroperfusion was used with the possibility of pressure-controlled retroperfusion at higher flows (1). Furthermore, reduced efficacy of synchronized coronary venous retroperfusion due to the characteristic anatomy of pigs with the azygos vein draining into the coronary sinus was avoided in this study by proper positioning of the retroperfusion catheter tip in the great cardiac vein (see Methods).

Effect of selective synchronized suction and retroinfusion of coronary veins and synchronized coronary venous retroperfusion on regional myocardial function and myocardial oxygen tension. The main finding of the present study was that selective synchronized suction and retroinfusion of coronary veins was able to significantly reduce loss of regional and global myocardial function (Fig. 4A, Table 1) during ischemia in the pig model. Mean subendocardial segment shortening (21% before ischemia) was preserved at 15% during min 1 of ischemia and at 11% between min 3 and 10 of ischemia (Fig. 4A), whereas systolic dyskinesia developed in pigs supported by synchronized coronary venous retroperfusion (Fig. 4B). The higher efficacy of selective synchronized suction and retroinfusion of coronary veins compared with that of synchronized coronary venous retroperfusion in reducing loss of regional myocardial function in the center of the ischemic zone was observed with the use of similar diastolic peak and mean coronary venous pressures during the pumped beats (Table 3). However, the catheter tip position was different between the two groups (Fig. 1). In pigs treated with selective synchronized suction and retroinfusion of coronary veins, the retroinfusion volume could be pumped selectively into the vein draining the ischemic zone because the suction device drained the venous system before each pumping period, thereby reducing residual blood volume and coronary venous pressure (Fig. 2). In contrast, an approach similarly close to the ischemic myocardium was not possible with the use of synchronized coronary venous retroperfusion. Retrograde catheterization was restricted to veins of sufficient size (i.e., great cardiac vein [see Methods]) to maintain venous drainage around the balloon at the catheter tip by systolic squeezing.

Although the residual blood volume was not actually measured in this study, it was indicated to be higher during synchronized coronary venous retroperfusion because a higher minimal coronary venous pressure was observed (Table 3). Conversely, a lower residual blood volume in the venous system before each pumping stroke using selective synchronized suction and retroinfusion of coronary veins

would also explain why similar retroinfusion volumes/beat could be delivered at similar peak and mean diastolic pressures (Table 3) despite the closer position of the catheter tip. Thus, it can be assumed that the retroinfusion volume delivered to the ischemic myocardium/beat was greater with the use of selective synchronized suction and retroinfusion of coronary veins than with synchronized coronary venous retroperfusion. However, the prerequisite to make this possible was to combine an active suction with a more selective retroinfusion. Therefore, from our data we cannot infer whether suction or a closer position of the catheter tip, or both, caused the improved preservation of myocardial function during ischemia in pigs treated by selective synchronized suction and retroinfusion of coronary veins.

During reperfusion, there was only a trend toward improved recovery of regional myocardial function in the pigs treated by retroinfusion during ischemia (groups A and B) compared with findings in control pigs (Fig. 4). Furthermore, the higher preservation of regional myocardial function and myocardial oxygen tension during ischemia in group A (Fig. 4) did not result in improved recovery during reperfusion compared with that in group B. One possible explanation for these unexpected findings is that the duration of ischemia (10 min) was too short to induce such a degree of myocardial dysfunction during reperfusion that differences among the three groups could be observed.

The pigs treated with synchronized coronary venous retroperfusion had a higher incidence of ventricular fibrillation in the early reperfusion period than that in group A (p = NS) (Table 2). Our measurements, including myocardial oxygen tension, cannot explain this observation. Because ventricular fibrillation was treated successfully within <30 s in all pigs, the recovery of regional myocardial function and myocardial oxygen tension during reperfusion (Fig. 4 and 5) was not altered by the occurrence of ventricular fibrillation (Table 2).

Recently, retrograde perfusion was induced in a pig model by nonsynchronous perfusion of the anterior ventricular vein combined with simultaneous venting of the left anterior descending coronary artery to zero pressure (22). With this approach, which is not applicable in clinical use, it was demonstrated that regional myocardial function determined by wall thickening could be maintained at 48% to 62% of baseline value at flow rates between 42 and 56 ml/min. These data are quite similar to the results obtained with the use of selective synchronized suction and retroinfusion of coronary veins during ischemia in the present study (Fig. 4A). This observation might indicate that selective synchronized suction and retroinfusion of coronary veins resulted in oxygen delivery and nutrient exchange as similar to that achieved by actual retrograde perfusion (22). As discussed in detail (22), during retroperfusion a considerable amount of blood (>70%) was shunted through venovenous interconnections or the thebesian system, although regional myocardial function improved to a similar extent at smaller flows with retroperfusion compared with anterograde perfusion. In both studies it cannot be excluded that retrograde perfusion had a different mechanical effect on regional myocardial function than anterograde perfusion. Thus, the "Gregg phenomenon" (i.e., the hypothesis that increases in coronary perfusion pressure increase ventricular performance independently from providing enhanced oxygen supply [23]) cannot be ruled out as contributing factor during retroinfusion, although it seems to play a minor role during anterograde perfusion in pigs (23).

Selective synchronized suction and retroinfusion of coronary veins seemed to increase the amount of retroinfused blood participating in nutrient exchange compared with synchronized coronary venous retroperfusion. This assumption was not only supported by the data of myocardial function (Fig. 4A) but also by the observation that mean myocardial surface oxygen tension was maintained >0 in the pigs supported by selective synchronized suction and retroinfusion of coronary veins (Fig. 5A). Myocardial surface oxygen tension is not representative of the transmural distribution of myocardial oxygen tension (24). Therefore, intramyocardial oxygen tension within midmyocardial layers (4) was measured in this study. Myocardial surface oxygen tension, midmyocardial oxygen tension and subendocardial segment shortening were less reduced in pigs supported by selective synchronized suction and retroinfusion of coronary veins during ischemia than in groups B and C (Fig. 4 and 5). This finding indicates that different layers of the myocardium (subepicardium, midmyocardium, subendocardium) were reached by the blood delivered retrograde during treatment by selective synchronized suction and retroinfusion of coronary veins and suggests a rather homogeneous supply by retroinfusion. However, the definite distribution of the blood delivered retrograde requires determination by regional blood flow measurements.

The efficacy of synchronized coronary venous retroperfusion to maintain regional myocardial function during ischemia was very low in this study, which is in agreement with previous studies in pigs (12,13,21). Apparently, nutritive blood flow, which was demonstrated to be induced by synchronized coronary venous retroperfusion in dogs and humans (1–3,23), was not sufficient to prevent loss of myocardial function in pigs. This difference might be explained by a higher residual arterial blood flow through collateral vessels into the ischemic zone in dogs (15) and patients with coronary artery disease than in pigs during acute occlusion of the left anterior descending coronary artery (11). Thus, a similar increase in oxygen delivery and nutrient exchange by retroinfusion might induce a different preservation of regional myocardial function in dogs and humans compared with pigs. Smaller sizes of the retroperfusion catheters might allow closer approach to the ischemic myocardium but would also reduce maximal flow rates (1). The imminent limits of synchronized coronary venous retroperfusion to selectively retroinfuse coronary veins, however, are determined by the necessity of venous drainage around the catheter tip.

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Clinical implications of the study. The pig model of occlusion of the left anterior descending coronary artery during a brief (10 min) period was used to simulate ischemia occurring in patients during coronary angioplasty with prolonged balloon inflation or abrupt closure of the artery after balloon inflation. Both methods of retrograde support during ischemia (selective synchronized suction and retroinfusion of coronary veins and synchronized coronary venous retroperfusion) appeared to be safe for clinical application with respect to damage to coronary veins and myocardial tissue. The efficacy of selective synchronized suction and retroinfusion of coronary veins, however, to prevent the decline of regional myocardial function and myocardial oxygen tension during ischemia was substantially higher than the efficacy of synchronized coronary venous retroperfusion. Extrapolation of animal data to humans must be applied with caution. However, the results of this study suggest that the efficacy of retroinfusion during coronary angioplasty in patients may be increased by performing selective synchronized suction and retroinfusion of coronary veins. Preservation of >50% of baseline regional myocardial function without a reduction of cardiac output during 10 min of ischemia in pigs (Fig. 4A, Table 1) might indicate that in patients supported by selective synchronized suction and retroinfusion of coronary veins, prolonged balloon inflation during coronary angioplasty will be feasible with only minor effects on regional and global myocardial function.

Study limitations. Limitations of the application of selective synchronized suction and retroinfusion of coronary veins in patients can be assumed because of the necessity of selective catheterization of the veins draining the ischemic zone. Catheterization of the anterior ventricular vein should be possible and sufficient to retroinfuse the ischemic zone in most patients with stenosis of the left anterior descending coronary artery (1). During percutaneous angioplasty of the left circumflex coronary artery, however, selective synchronized suction and retroinfusion of coronary veins might be less effective than synchronized coronary venous retroperfusion if more than one vein is draining the ischemic zone. This is the case in approximately 25% of humans (24). Furthermore, long-term application of selective synchronized suction and retroinfusion of coronary veins might be more difficult than synchronized coronary venous retroperfusion because the suctioned blood must be reinfused or replaced. Reinfusion of the blood and the use of synthetic oxygen carriers for selective synchronized suction and retroinfusion of coronary veins are currently under investigation. For the reasons mentioned previously, selective synchronized suction and retroinfusion of coronary veins and synchronized coronary venous retroperfusion do not exclude each other. In contrast, a retroinfusion device allowing the performance of either selective synchronized suction and retroinfusion of coronary veins or synchronized coronary venous retroperfusion should provide the highest flexibility for retrograde support of coronary angioplasty of normal duration and prolonged ischemia as well as in high risk and unsuccessful coronary angioplasty.

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